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REVIEW

Lubiprostone for the Treatment of Adult Women with Irritable Bowel Syndrome with Constipation

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Abstract: Irritable bowel syndrome with constipation (IBS-C) affects approximately 5% of the population in western countries. The majority of those afflicted are women. Symptoms are often detrimental to the individual's quality of life and incur high healthcare costs to society. There is no evidence to support changes in lifestyle, laxatives or over the counter supplements. Tegaserod appeared to have promising results but was promptly removed from the market due to adverse cardiovascular events. In 2008, lubiprostone (Amitiza) was approved by the US Food and Drug Administration (FDA) for the treatment of women with IBS-C. It is thought to selectively activate type 2 chloride channels in the apical membrane of the intestinal epithelial cells leading to chloride secretion. As result, sodium and water are passively secreted generating peristalsis and laxation, without stimulating gastrointestinal smooth muscle. Several trials with predominantly female patients have shown it to be effective in the treatment of IBS-C. Overall lubiprostone was safe, well tolerated and associated with mostly benign side effects. Nausea and diarrhea were the most commonly reported. Though there are no head to head comparisons with other pharmacological agents, it is our opinion that lubiprostone should be tried as a first line pharmacotherapy for women with IBS-C at a dose of 8 µg BID. Thus far, lubiprostone offers a welcome approach to our narrow therapeutic armamentarium. Further understanding of its mechanism of action may provide additional insight into the pathophysiology of IBS-C.

Keywords: lubiprostone, IBS-C, women, chloride channel 2

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Introduction

Rome III defines irritable bowel syndrome as recurrent abdominal pain or discomfort occurring for more than 3 days per months for the past 3 months. Symptom duration should exceed 3 months with onset occurring at least 6 months prior to diagnosis. Symptoms must be associated with two or more for the following: improvement with defecation, onset associated with change in stool frequency and form (Table 1). IBS-Constipation is further characterized by having hard or lumpy stools accounting for at least 25% of defecations; loose or watery stools consisting of no more than 25% of defecations. Based on Rome III criteria, the prevalence of IBS is thought to lie between 5%–15%, whereas that of IBS-C approximates 5%[1] (Table 2). The incidence remains difficult to estimate as symptoms are often intermittent and many do not seek medical attention.[1] Gender disparity is a recognized phenomenon in IBS with women being affected up to twice as much as men in western countries. Studies indicate that most women with IBS are found to have IBS-C and some reports suggest that this may account for all the female gender bias in IBS.[2] When symptoms are severe, IBS becomes detrimental to all aspects of daily life, generating stress, anxiety and depression. Absenteeism from work and decrease in productivity are frequently reported. In the United States alone, the annual economic burden of IBS is estimated to be $20–$25 billion.[3]

Patients with IBS-C often resort to over the counter fiber supplements, probiotics and laxatives with no significant improvement in overall symptoms and quality of life. Furthermore, evidence to support these measures is lacking. With respect to the use of Polyethylene glycol for IBS-C, the ACG task force concludes that it was shown to improve stool frequency but not abdominal pain based on a study consisting of post pubertal adolescents, 59% of which were female.[4] Pharmacotherapy for this condition remains limited. In 2002 the FDA approved tegaserod, a selective 5 HT4 receptor agonist for short-term use in women with IBS-C. Several clinical trials showed it to be superior to placebo at improving global IBS symptoms, abdominal pain, stool frequency, consistency, straining and bloating.[4] Due to reports of adverse cardiovascular events, tegaserod was suspended from the North American market in 2007 and completely withdrawn by 2009. In April 2008, the FDA approved lubiprostone for the treatment of women with IBS-C after several studies showed favorable outcomes. This article reviews lubiprostone's mechanism of action, pharmacokinetic properties and evidence-based data pertaining to efficacy and safety profile in female subjects with IBS-C.

Table 1. IBS—definition (Rome III).

At least 12 weeks, which need not be consecutive, in the preceding 6 months of:
Abdominal pain/discomfort associated with two or more of the following: • Altered stool frequency • Altered stool consistency • Relieved with BM
May also be associated with: • Bloating, feeling of abdominal distension, passage of mucus, straining • Incomplete evacuation • May alternate with diarrhea

Longstreth et al. *Gastroenterology*. 2006.

Table 2. Prevalence of IBS sub-types.

IBS sub-type	Prevalence
IBS-C	5.2%
IBS-D	5.5%
IBS-M	5.2%

ClC—Channels

Chloride channels are protein pores located in cells throughout the body.[5] They are involved in the transport of ions and fluid across many epithelial membranes. Their main functions include fluid transport and secretion, regulation of cell volume and pH, and maintenance of cell membrane potential.[6] ClC channels are involved in chloride secretion. A total of 9 subtypes of ClC have been described.[5]

The ClC type 2 channels are distributed in tissues throughout the body. In the intestines they are expressed both on the apical surface of the epithelium as well as on the basolateral side. Another important type of chloride channel that is involved in the control of water and chloride secretion in the body is the cystic fibrosis transmembrane conductance regulator (CFTR). Dysfunction of CFTR results

in impaired trans-epithelial transport that occurs in cystic fibrosis.[7,8]

Lubiprostone

Pharmacokinetics and mechanism of action

Pharmacokinetics

Lubiprostone (Amitiza®) (Sucampo Pharmaceuticals, Bethesda & Takeda Pharmaceuticals of North America, Chicago, IL) is a bicyclic fatty acid derived from a metabolite of prostaglandin E_1 (PGE_1).[7,9] It does not appear to have any action on prostaglandin E or F receptors.[10] It has prompt onset of action and low systemic bioavailability following oral intake. Absorption from the gut is poor and the drug is readily metabolized. M3 is the only detectable metabolite in the blood and results from the rapid action of carbonyl reductase in the apical lining of the stomach and jejunum.[11] M3 is 94% bound to plasma protein and has a half life of 0.9 to 1.4 hours. Lubiprostone is not metabolized by the hepatic cytochrome P450 pathway. Animal studies using radio labeled lubiprostone have shown that most of the drug is cleared within 48 hours. Lubiprostone does not alter colonic motor activity, and is unlikely to shorten colonic transit time.[12] Additionally, lubiprostone may enhance intestinal barrier function and prevent acid related injury to the duodenum.[11] Increased gut permeability along with inflammatory cells within the intestinal epithelium are thought to play a role in the pathophysiology of IBS.[13,14]

Mechanism of action

Lubiprostone induces intestinal fluid secretion via activation of ClC-2 channels located on the apical side of intestinal epithelial cells present throughout the gastrointestinal tract.[7,15] The opening of Cl^- channels in the small and large intestinal epithelium results in chloride secretion as well as bicarbonate (HCO_3^-) secretion in the duodenum.[16] Sodium and water passively follow resulting in fluid secretion into the bowel lumen. Bijvelds et al further investigated lubiprostone's mechanism of action since activation of ClC-2 channels is thought to benefit constipation related to cystic fibrosis. After measuring Cl transport in 3 model systems, lubiprostone did not induce intestinal Cl^- secretion in CFTR-null mice and tissue of cystic fibrosis patients.[17] This led the investigators to conclude that lubiprostone enhances intestinal Cl^- and fluid secretion by activating CFTR through prostanoid receptor signaling, and thus led to controversy whether its action is directly at ClC-2 channels or CFTR channels or both, due to the fact that earlier reports had shown no effect on CFTR channels in human cell lines transfected with recombinant human CFTR.[7] Though, most evidence supports ClC-2 channel activation, the exact mechanism of action of lubiprostone remains controversial.

Additional properties of lubiprostone pertaining to visceral sensitivity and gut motility have been recently investigated. Whitehead et al assessed the effects of lubiprostone on pain thresholds in patients with IBS-C in a double blind randomized cross-over trial. Predominantly female subjects (85.5%) were randomly assigned to one of two test arms. One group received 2 weeks of lubiprostone (24 µg BID) followed by a 2-week washout period, and then took placebo capsules for 2 weeks. The other group started with 2 weeks of placebo capsule followed by a 2-week washout, and ended 2 weeks of lubiprostone therapy (24 µg BID). Clinical symptoms were assessed throughout the study with daily symptoms ratings, and IBS severity scale (categorizes symptoms as mild, moderate, or severe). Those questionnaires were completed at the end of the baseline period and at the end of each of the two intervention periods. Furthermore, gut transit time and pain sensitivity (using barostat testing) were assessed at the end of each intervention period.

The principal finding of this study is that lubiprostone does not have a significant impact on the sensory thresholds for pain or urgency to defecate, and does not alter transit time (as measured by colonic sitzmark study). The study concludes that pain reduction reported in trials of lubiprostone is unlikely to be due to changes in pain sensitivity. The author's data suggests that reduction in clinical pain may be due to changes in stool consistency, whereby softer stools may reduce the frequency with which the lumen of the bowel is distended sufficiently to induce pain.[18] In 2008, the FDA approved lubiprostone at a dose of 8 µg BID for the treatment of IBS-C in adult women. The drug should preferably be administered with food in order to lower the incidence of nausea.

Clinical Efficacy

Irritable bowel syndrome-Constipation (IBS-C)

Currently in the literature there are no gender specific studies evaluating the drug's efficacy, hence all studies have a male and female cohort. Several clinical trials, consisting predominantly of Caucasian female patients have substantiated its efficacy. Johanson et al evaluated 195 patients (91% females) meeting Rome III criteria for IBS-C in a phase 2 multi-center dose finding study[19] (Table 3). Patients were assigned to 4 treatment arms consisting of twice a day doses of 8, 16, 24 μg or placebo for 3 months. After one month, those who received lubiprostone showed greater improvement in abdominal pain and/or discomfort scores, which represented the primary end point. Secondary endpoints comprised of frequency of spontaneous bowel movements, stool consistency, straining, and bloating. After two months, all three drug doses showed greater improvement in abdominal pain/discomfort scores ($P \leq 0.039$). After three months of treatment, although the improvement in abdominal pain and/or discomfort was greater in the lubiprostone arm, it did not reach statistical significance compared to placebo. Patients receiving all doses of lubiprostone experienced greater reduction in straining, bloating, stool frequency, stool consistency, and severity of constipation but the differences were not statistically significant. The 24 μg BID treatment arm had the greatest improvement in symptoms as well as greatest number of adverse effects. The data from this trial indicates that lubiprostone 8 μg twice a day offered the best compromise between efficacy and tolerability.

A similar phase-2, double-blind, randomized, placebo-controlled, and dose-finding study for the treatment of patients with constipation (with or without IBS) included a total of 170 patients who received 16 μg, 32 μg, or 48 μg or placebo daily for a total of 2 weeks. Subjects were predominantly females (90.6%) who met Rome III criteria for chronic idiopathic constipation either with or without IBS-C. The primary efficacy end point was change from baseline in weekly average spontaneous bowel movements (SBM) at 1 week. Secondary efficacy end point was change in the weekly average number of SBM at week 2. Subjects assigned to lubiprostone treatment arms had higher SBM frequency compared with placebo at the time of both primary and secondary end points. Subjects with IBS-C showed a significant increase in SBMs with 48 μg lubiprostone at week 1 ($P < 0.05$), but with more side effects at this dosage. Due to the short time frame of the study, there was no statistical difference in quality of life (QOL) as measured by the SF-36 and IBS-QOL between lubiprostone and placebo.[20]

Two phase 3, multicenter, randomized trials of lubiprostone 8 μg BID vs. placebo included 1171 subjects who met Rome II criteria for IBS-C. Subjects were asked to report their relief in IBS symptoms in the last week compared to how they felt before entering the study. The subjects reported improvement in symptoms using a balanced seven-point Likert scale extending from significantly relieved (+3), to significantly worse (−3). Subjects who were moderately relieved for 4 consecutive weeks or significantly relieved during at least 2 out of 4 weeks of the months were considered monthly responders.

The primary efficacy endpoint was the percentage of overall responders that were at least moderately relieved for all 4 weeks of the month or significantly relieved for at least 2 weeks of the month. Those who were monthly responders for at least 2 of the 3 months of the study were considered overall responders. Subjects who received lubiprostone were more likely to respond compared with subjects who received placebo (17.9% vs. 10.1%, $P = 0.001$). The incidence of adverse events was comparable in both groups.

In conclusion, the investigators found that significantly more subjects treated with lubiprostone 8 μg BID were overall responders compared to those treated with placebo. Lubiprostone was well tolerated and associated with a favorable safety profile[21] (Table 3).

Furthermore, lubiprostone improved the quality of life in subjects with IBS-C, according to the IBS-QOL questionnaire. Clinically relevant improvements were observed with respect to social reaction, food avoidance, health worry, body image, and dysphoria.

Safety and tolerability

Chey et al determined long term safety, tolerability, and occurrence of adverse events in 522 subjects, predominantly females (93%) with IBS-C who received lubiprostone 8 μg, twice daily for 36 weeks. No serious

Table 3. Clinical studies of Lubiprostone for the treatment in IBS-C.

	Study type		Patients			Interventions	Key results
	Design	Duration	N	Age	Females (%)		
Chey et al[3]	Extension study of two randomized placebo controlled phase 3 studies. Assessment of long term safety and tolerability	36 weeks	522	47.2	93%	Lubiprostone 8 μg bid	Overall incidence of treatment related adverse events was 25.4%. Diarrhea and nausea were the most common
Johanson et al[19]	Randomized, double-blind, placebo-controlled, multicenter, phase 3 trial	3 months	195	48.6	90%	Lubiprostone 8, 16, 24 μg bid	After 1 month, lubiprostone showed greater improvements in mean abdominal discomfort/pain scores vs. placebo ($P = 0.023$). After 2 months, all lubiprostone groups showed significantly greater improvements in mean abdominal discomfort/pain scores ($P = 0.039$). After 3 months of treatment, the improvement in each lubiprostone arm was greater than placebo, but the test for trend was no longer significant
Drossman et al[21]	2 randomized, double blind, placebo controlled, multicenter, phase 3 trial	12 weeks	1171	46.6	92%	Lubiprostone 8 μg bid vs. placebo	Higher percentage of lubiprostone-treated patients were overall responders compared with placebo (17.9% vs. 10.1%, $P = 0.001$). Similar incidence of adverse events between both groups

adverse events related to the drug were observed. Over the duration of the study there were no significant changes in vital signs or changes from baseline laboratory values. 21 out of the 522 subjects (4%) discontinued lubiprostone due to adverse effects. 41 subjects (7.9%) decreased their dose due to adverse events, 4 of which eventually discontinued the medication all together. The overall incidence of treatment related adverse events was 25.4%. Diarrhea (11.0%), nausea (11.0%), and abdominal distention (5.8%) were the most common side effects related to lubiprostone.

Of the subjects that developed diarrhea, most were mild to moderate in severity and lead to 6 (1.2%) subjects discontinuing its use. Similarly, 3 (0.6%) subjects stopped lubiprostone as result of nausea. Based on these results the authors showed that for subjects with IBS-C, lubiprostone 8 µg twice a day was safe and well tolerated over 13 months of use[3] (Table 3).

Prior studies have also reported similar side effect profiles. Nausea (8%), diarrhea (7%), and abdominal pain (5%) were the most common adverse effects in those receiving lubiprostone 8 µg twice daily for IBS-C (Table 3). These adverse effects were comparable in double-blind phase 2 and phase 3 and in open label long-term studies[19] (Table 3).

How lubiprostone results in nausea is not well understood. Small bowel distention following increase fluid secretion may contribute in part. There were no reported electrolyte abnormalities associated with the occurrence of diarrhea. As most cases were mild to moderate, this could explain the absence of electrolyte imbalance.[21] Although no dosage adjustment is required in patients with renal impairment, recent FDA recommendation and product package insert recommends that patients with Childs-Pugh A require no dose adjustment, whereas those with moderate hepatic impairment (Child—Pugh Class B) should be prescribed a maximum of 16 µg BID and those with severe hepatic impairment should receive a maximum dose of 8 µg BID.[22] These recommendations are mainly intended for the chronic constipation population that requires dosage up to 24 µg BID. The FDA recommended dosage for the IBS-C population is limited to 8 µg BID. There are no known drug-drug interactions identified to date.

A study evaluating lubiprostone 24 µg BID to placebo for a period of 4 weeks in 237 subjects (119/118) with chronic constipation showed that the most common adverse events were nausea (21%), abdominal pain (6.7%) and dyspnea (3.4%). A total of 15 lubiprostone-treated subjects (12.6%) and 1 placebo subject (0.8%) discontinued treatment early. Among the lubiprostone subjects who discontinued early, the most common adverse events were nausea 2.5% (6/15) and abdominal pain 1.3% (3/15). There were no serious adverse events associated with the drug and no subject deaths during the study, furthermore, no clinically relevant changes in laboratory values, vital signs or physical examination findings were noted.[23]

Johanson et al had assessed the long term safety and efficacy of lubiprostone in IBS-C. Subjects who demonstrated more than 70% compliance with the medication in the phase 3 studies were enrolled in the study. Lubiprostone was effective and well tolerated in adults with IBS-C throughout 48 weeks of treatment. The side effect profile in the placebo controlled and long term open studies were similar. The incidence of treatment related serious adverse events (1% in each group) and adverse events (22% vs. 21%) compared to placebo were similar. The only serious adverse event reported was non-cardiac chest pain which resolved with discontinuation of the medicine. The most common adverse events compared to placebo were nausea (8% vs. 4%), diarrhea (6% vs. 4%), and abdominal pain (4% vs. 5%)[19,21] (Table 4).

Dyspnea has been reported in a few studies, with a prevalence of 0.4%. Although rare, this side effect typically occurred within an hour of the first dose, lasted no more than a few hours and often recurred with further use. When dyspnea occurred, subjects described as chest tightness and difficulty breathing. Dyspnea was generally self-limited and not considered as serious adverse event.[24] It remains unclear as to how lubiprostone causes dyspnea. In vitro studies have demonstrated that lubiprostone can activate chloride secretion when applied topically on respiratory

Table 4. Most common adverse reactions.

Adverse reaction	Lubiprostone (8 µq twice daily) n = 1011	Placebo
Nausea	8%	4%
Diarrhea	7%	4%
Abdominal pain	5%	5%
Abdominal distention	3%	2%

epithelial tissue.[25] Until better understanding of the underlying mechanism, lubiprostone should be discontinued in subjects who develop dyspnea.

Pregnancy and Lactation

Lubiprostone is classified as pregnancy category C, ie, animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans. Women of childbearing age should have a negative pregnancy test prior to initiating therapy. Its use during pregnancy can only be justified if the benefits outweigh the risks to the fetus.[23] It is not clear whether lubiprostone is excreted in human milk.

Conclusion

Lubiprostone at a dose of 8 μg BID is currently approved by the FDA for the treatment of women age 18 and above with IBS-C. Several studies have validated its efficacy and its use has consistently been associated with favorable outcomes. The majority of subjects in all studies were females. Based on long term studies lubiprostone is safe and generally well tolerated, and has not been associated with any life threatening events. Pregnant women or those contemplating pregnancy should not take lubiprostone. Drug safety has been evaluated for a period of up to 13 months, and currently there are no limitations on duration of treatment, however, the indication should frequently be reassessed. The most common side effects are nausea, diarrhea, bloating and dizziness. Lubiprostone is currently an excellent treatment option for IBS-C. A recent review of evidence based data by a panel of gastroenterologists favors the use of lubiprostone as a first-line therapy in the treatment of female subjects with IBS-C at a dose of 8 μg twice daily.[26]

Author Contributions

Conceived and designed the experiments: RS. Analysed the data: MS, RS. Wrote the first draft of the manuscript: MS. Contributed to the writing of the manuscript: RS. Agree with manuscript results and conclusions: RS. Joinly developed the structure and arguments for the paper: MS, RS.

Conflict of Interests

The authors disclose no conflicts.

Disclosures and Ethics

As a requirement of publication author(s) have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest. Provenance: the authors were invited to submit this paper.

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